
Comparative Binding Energetics of Mg^{2+} , Ca^{2+} , Zn^{2+} , and Cd^{2+} to Biologically Relevant Ligands: Combined *Ab Initio* SCF Supermolecule and Molecular Mechanics Investigation*

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ABSTRACT

A combined *ab initio* SCF supermolecule and molecular mechanics investigation is carried out on the binding energetics of the divalent cations Mg^{2+} , Ca^{2+} , Zn^{2+} , and Cd^{2+} to a series of the most common ligand functional groups found in biomolecules. The SCF binding energy components are resolved using the restricted variational space method.¹ The results show that the SIBFA molecular mechanics (SMM) procedure² reproduces the *ab initio* binding energies and total energy variations as a function of intermolecular variables. The model also reproduces the selectivity energetics for exchange reactions. Thus, the SMM procedure can be used without reparametrization to describe the coordination energetics of complex molecules including those subject to coordination changes. The energetic properties of divalent cation–hexahydrate complexes are compared as examples of a complete, realistic coordination system. The hexahydrates exhibit strong nonadditive effects typical of dication coordination. Nevertheless,

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Introduction

The divalent cations Mg^{2+} , Ca^{2+} , and Zn^{2+} exert a prominent role in the structural stability of biopolymers, and also act as critical cofactors within the active site of metalloenzymes. Proteins and nucleic acids are able to discriminate between divalent cations with a high degree of selectivity. Thus, although the following list is by no means exclusive, Zn^{2+} is the cation conferring its specific structural pattern to the zinc-finger class of transcriptional activating proteins, and nerve growth factor, whereas Ca^{2+} is the cation preferentially bound to a family of related proteins, encompassing calmodulin, troponin C, calbindin, oncomodulin, and parvalbumin. It is also involved in the stabilization of interprotein complexes, as occurs in a cascade of thrombin-induced events, or in cellular adhesion. In nucleic acids, Mg^{2+} is, among closed-shell divalent cations, the one most frequently encountered in tRNA structural stabilization. When it binds to DNA, Mg^{2+} is located preferentially along the phosphodiester backbone, whereas Zn^{2+} binds in the major groove, to the purine bases. Zn^{2+} is the metal cofactor of the enzymes carboxypeptidase, carbonic anhydrase, enkephalinase, and the general class of matrilysin proteases. Mg^{2+} is the cofactor of a series of G-proteins and their oncogenic p21 mutants, and is also involved in ribozyme catalysis. Ca^{2+} is the cofactor of phospholipases A and C as well as of a class of nuclease enzymes. Because its nucleus has a magnetic moment, Cd^{2+} is often used as a surrogate for Zn^{2+} in NMR experiments [see Refs. 3(a)–(c) for review].

An understanding of the energetical basis for such a diverse pattern of selectivity between divalent cations is warranted. Let us consider, besides water itself, the most conspicuous ligands which are involved, within a binding cavity, in the polyligation of the metal cation. These are formamide (for the peptide backbone and the Asn and Gln side chains); formate (for the side chains of aspartate and glutamate); hydroxy, which can be generated after cation-induced deprotonation of a water molecule; imidazole (for the histidine side chain);

methanethiol and methanethiolate (for protonated and deprotonated cysteine side chains); and methoxy (involved as the alkoxy group in transition state intermediates). The modulation of affinities of a given ligand for a series of divalent cations was originally given an interpretation in terms of softness/hardness of the interacting acid–base pair (HSAB).⁴ Predictions made on the HSAB concept can be made, however, in qualitative terms only for some types of exchange reactions. A more quantitative understanding was offered recently by our group on the basis of high-level *ab initio* SCF supermolecule computations bearing on the various M^{2+} –ligand complexes.⁵ By resorting to the restricted variational space analysis developed by Stevens and Fink,¹ a breakdown of the total intermolecular interaction energy, ΔE , into separate components was performed, namely coulomb (E_c), exchange (E_e), polarization (E_{pol}), and charge transfer (E_{ct}). Upon resuming the SCF computations at the MP2 level, numerical values for the correlation energy contribution in these complexes were further provided. This enabled tracing back of the differences in binding affinities for a given ligand, of two cations belonging to either the two distinct groups IIA and IIB (i.e., “soft” versus “hard”), or to one and the same group (i.e., “size selectivity”), to well-defined energy contribution(s).

An essential objective of the present work will be, with the prospect of large-scale computations of cation–oligopeptide complexes, to assess the ability of the SIBFA molecular mechanics procedure^{6,7} (denoted as SMM in what follows) to reproduce the results and numerical trends of the *ab initio* computations. Recent refinements to this procedure were detailed in an earlier study devoted to a series of Zn^{2+} –ligand complexes.² The present investigation extends the applicability of the SMM procedure to Mg^{2+} , Ca^{2+} , and Cd^{2+} . In keeping with Ref. 2, and as a complement to our earlier *ab initio* SCF/MP2 study devoted to these four cations,⁵ we will now also probe, in more detail, for a series of representative complexes, the dependencies of *each* of the separate *ab initio* components $E_1 = E_c + E_e$, E_{pol} , and E_{ct} , as a function of radial or angular variations of the cations, and how well these can be reproduced by their corre-

sponding SMM counterparts. If satisfactory representations of these energetics are achieved, the SMM procedure could then be used to make quantitative predictions of detailed properties including those not related to HSAB.

The present results will be presented in the following manner. We will first collect the SMM/SCF results obtained for Mg^{2+} , Ca^{2+} , and Cd^{2+} binding to the neutral and anionic ligands of interest in this study, the Zn^{2+} results having been presented in detail in our previous investigation.² For representative complexes, the trends in the evolutions of the separate SCF and SMM energy components will be analyzed and compared. A comparison between the individual values of the correlation energy at the MP2 level and those of E_{disp} (SMM) will then be separately carried out in the case of the two IIB cations, Zn^{2+} and Cd^{2+} . A representative polyligated complex of each of the four divalent cations will be considered next, namely M^{2+} surrounded by six water molecules in a regular octahedron arrangement. A comparison between the SCF/MP2 and SMM results will be done. In the last part of this study, we will focus on three selected pairs of cations, namely Zn^{2+} versus Mg^{2+} , Mg^{2+} versus Ca^{2+} , and Zn^{2+} versus Cd^{2+} . For each pair, we will analyze the evolutions, as a function of the bound ligand, of representative energy differences between their SMM components at their respective equilibrium distances. The ligands will be ranked in the same ordering as in our original SCF/MP2 analysis.⁵

Procedure

AB INITIO SUPERMOLECULE INTERACTIONS

For the various cation–ligand complexes of interest in our study, the *ab initio* SCF supermolecule procedure represents the most reliable means of obtaining numerical values for the intermolecular interaction energy values ΔE and probing their radial and angular dependencies. To develop a properly transferable functional form to represent the total ΔE s in molecular mechanics, a deconvolution of ΔE into its separate components is warranted. Any successful reproduction of the *ab initio* results could only be ensured if such individual components could *each* have a formulation of its own in molecular mechanics procedures.

Consistent with our earlier investigations,^{2,5,8} we have performed energy decomposition at the

supermolecule level using the restricted variational space procedure of Stevens and Fink.¹ Four computations are performed, providing, respectively: the intermolecular interaction energy with the cation orbitals frozen ΔE (SCF); the separate coulomb energy (E_c); the first-order energy ($E_1 = E_c + E_e$) obtained upon freezing the occupied orthogonalized MOs of all interacting entities, which includes the exchange contribution E_e , whence $E_2 = \Delta E_f - E_1$; and the ligand polarization energy (E_{pol}), obtained upon relaxing the occupied and virtual MOs of the cation, whence $E_{\text{ct}} = E_2 - E_{\text{pol}}$. In addition to these computations, we will refer, at equilibrium positions, to the values of the MP2 correlation energy (E_{corr}) which were published in Ref. 5 by our group, and to which we will compare those of E_{disp} (SMM) in what follows.

The basis sets used are the same as those used previously.^{5,8} Let us recall that, for H, C, N, O, and S they correspond to the CEP/4-31G basis sets derived by Stevens et al.,⁹ supplemented on the heavy atoms by two diffuse, uncontracted 3*d* orbitals, the exponents of which were given in Refs. 2 and 5. The Zn and Cd core electrons are, correspondingly, replaced by coreless effective potentials.⁹ The outer-shell 3*sp* orbitals of Zn^{2+} are represented by eight Gaussians, contracted (4,1,2,1), and the 3*d* orbitals are represented by six Gaussians, contracted (4,1,1). The outer-shell 4*sp* orbitals of Cd^{2+} also have eight Gaussians contracted (4,1,2,1), whereas the 4*d* orbitals have five Gaussians, contracted (3,1,1). All the *spd* exponents and expansion coefficients are those derived by Stevens et al.⁹ The basis sets used on Mg^{2+} is a full-electron 6-631G basis set,¹⁰ and that used on Ca^{2+} is a 6-6631G set, as discussed and detailed in Ref. 5. The divalent cations have two contracted *d* polarization functions, with exponents given in Ref. 5. The MP2 computations on Zn^{2+} and Cd^{2+} used an additional set of split *f* orbitals on Zn^{2+} and Cd^{2+} , having exponents of 0.9 and 0.63, respectively.⁵

Let us recall that following such an energy decomposition, E_{ct} (SCF), along with the correlation energy correction, E_{corr} , were shown earlier to be instrumental into favoring “soft” IIB over “hard” IIA cations of similar size, contributing an energy difference to the relative ΔE s that increase as a function of the “softness” of the ligand.⁵ E_{pol} (SCF) was found to be substantially less selective in this respect, conferring instead, in conjunction with E_1 (SCF), a selectivity in favor of the smaller cation in each of the separate IIA or IIB series.

MOLECULAR MECHANICS COMPUTATIONS

The intermolecular interaction energies are performed with the STBFA molecular mechanics (SMM) procedure,^{2,6,7} which expresses ΔE_{SMM} under the form of five separate terms:

$$\Delta E_{\text{SMM}} = E_{\text{MTP}} + E_{\text{rep}} + E_{\text{pol}} + E_{\text{ct}} + E_{\text{disp}}$$

The analytical expressions of these separate terms were provided in the original studies,^{6,7} and recent refinements presented in our study devoted to Zn^{2+} -ligand interactions.² We will briefly recall these as follows:

- E_{MTP} , the electrostatic (multipolar) term, is computed as a sum of multipole-multipole terms. The multipoles (up to quadrupoles) are derived from *ab initio* SCF computations on the individual ligands using the same Gaussian orbital basis sets as in the RVS computations, and are distributed on the atoms and chemical bonds making up the molecule following the procedure of Vigné-Maeder and Claverie.¹¹
- E_{rep} , the short-range repulsion, is computed as a sum of bond-bond, bond-lone-pair, and lone-pair-lone-pair interactions. The effect of hybridization is taken into account on both bond and lone-pair orbitals. Denoting by S an expression for the overlap between a cation-centered spherical density and the bond or lone-pair hybrid, E_{rep} is taken as proportional to S^2/R , where R denotes the distance between the latter's centroid and the cation.
- E_{pol} , the polarization energy, is computed with the help of distributed anisotropic polarizabilities, which are derived from the *ab initio* SCF wave function using the procedure developed by Garmer and Stevens.¹² Using the Boys localization criterion, the polarizabilities are localized on the centroids of the bond orbitals and lone-pair hybrids. The polarizing field is screened by a Gaussian function of the cation-centroid overlap.²

In the expression of E_{ct} , the charge-transfer contribution, an explicit coupling to the polarization is introduced. This is done essentially by means of an expansion of the effective radius of the electron

donor, proportional to the polarizing field and along its direction.²

As was shown in our preceding investigations dealing with oligated M^{2+} complexes,^{2,5,8} the nonadditive behavior of ΔE can be traced back, to a very large extent, to the second-order contributions E_{pol} and E_{ct} .

In the presentation of our results, consistent with the notations used for the SCF computations, we will denote, by E_1 (SMM), the sum: $E_{\text{MTP}} + E_{\text{rep}}$, and by E_2 (SMM) the sum: $E_{\text{pol}} + E_{\text{ct}}$.

- E_{disp} , the dispersion energy, is computed as a function of $1/R^{**6}$, $1/R^{**8}$, and $1/R^{**10}$ expansion, as formulated in Refs. 13 and 14. Each of these three terms is, furthermore, damped by an exponential damping factor. The effects of the lone pairs centered on the heteroatoms are simulated by resorting to fictitious atoms centered on the lone-pair centroids. The values of effective radii of the lone-pair bearer and lone-pair fictitious atoms, as adopted in the original articles,^{7(a,b)} are given in the Appendix. An explicit exchange-repulsion term is, furthermore, added to E_{disp} (see Refs. 13–15 for more details). For Zn^{2+} and Cd^{2+} , E_{disp} (SMM) was calibrated to reproduce the values of the MP2 correction in their respective water complexes at equilibrium distance. Because the MP2 correction was found to be very small in the case of Mg^{2+} and Ca^{2+} , E_{disp} (SMM) was not computed in their case. Note that E_1 , E_{pol} , and E_{ct} will be compared to their SCF RVS counterparts at the *uncorrelated* level. Thus, in the present approach, and that of Ref. 13, E_{disp} is identified as the difference between ΔE (MP2) and ΔE (SCF). The validity of this assumption will be assessed subsequently in the actual numerical tests.

Calibration

The calibration of the SMM procedure was presented in our studies devoted to Zn^{2+} -ligand² and H-bonded complexes.¹⁵ The only novel parameters to be introduced are thus those of the Mg^{2+} , Ca^{2+} , and Cd^{2+} cations (given in the Appendix). Their significance is given in the original articles.^{7(a,b)} With M denoting the divalent cation considered,

these parameters are:

- For E_{rep} , the effective radii, W , and the multiplicative factors $K(\text{M—H})$, $K(\text{M—C})$, $K(\text{M—O—N})$, $K(\text{M—O})$, and $K(\text{M—S})$. In addition, the \mathbf{m}_{PM} factors were rescaled.
- For E_{ct} , the effective radii, U , and the multiplicative factors S_{M} and D_{M} . In addition, the \mathbf{t}_{AsM} , \mathbf{t}_{ApM} , and \mathbf{m}_{AM} factors were rescaled.
- For E_{disp} , the multiplicative factors $L(\text{M—H})$, $L(\text{M—C})$, $L(\text{M—O—N})$, $L(\text{M—O})$, and $L(\text{M—S})$.

In keeping with Ref. 2, the values of these parameters for (a) and (b) were adjusted so that the corresponding SMM term matches the radial evolution of its SMM counterpart in the case of the M^{2+} complexes with water (O-ligand) imidazole (N-ligand), and methanethiol (S-ligand). The cation is located in the ligand plane, along the external bisector of the bound heteroatom, and variations of the M^{2+} -ligand distances are performed with a 0.1-Å amplitude close to the equilibrium distance.

The calibration of the L coefficients intervening in E_{disp} was done in such a way so that this term reproduces the values of the MP2 correction for these three ligands at equilibrium distance.⁵

For simplicity, we have set the same values for the \mathbf{m}_{PM} , \mathbf{m}_{AM} , \mathbf{t}_{AsM} , and \mathbf{t}_{ApM} for Cd^{2+} as for Zn^{2+} .² The values for Ca^{2+} and Mg^{2+} were modified from these and readjusted to refine the fit to the SCF values in the three above-mentioned examples. It should be noted at this point that the complexes employed in calibrating the SMM procedure² probably acquire open-shell characteristics at large coordination distances. This is due to the influence of asymptotic states in which an electron is transferred to the dication.¹⁶ The restricted Hartree-Fock wave function is unable to accurately represent this possible asymptote and intermediate partially open-shell states. However, in complete ligand shells, the influence of open-shell asymptotes should not be very large for these dications. Therefore, such effects are irrelevant to applications of the SMM procedure and are ignored in this work. Analysis of the MP2 contributions in our previous work also suggested that open-shell charge transfer effects were numerically unimportant at around the usual coordination distances.⁵ Dispersion effects appeared to be the most important adjustment necessary with respect to the Hartree-Fock states.

Results and Discussion

Mg^{2+} -, Ca^{2+} -, AND Cd^{2+} -LIGAND BINDING: COMPARISON BETWEEN SCF AND SMM RESULTS

The optimized divalent cation-ligand interaction energies and their individual components are given in Tables Ia (Mg^{2+}), Ib (Ca^{2+}), and Ic (Cd^{2+}). Throughout this article, figures and tables marked with an asterisk are available as supplementary material. We will now consider the separate M^{2+} -ligand complexes. Consistent with Refs. 2 and 8, the values of ΔE (SCF) reported here correspond to the cation core frozen. Numerical estimates for the energy increments gained upon relaxing the cation core are provided in Ref 5. The largest increments are those occurring with the monoligated complexes of Zn^{2+} and Cd^{2+} with anions and never exceed 2% of the binding energy. In addition, it was observed that, in model symmetrical polyligated complexes, such as $\text{M}^{2+}(\text{H}_2\text{O})_6$, their weight is further decreased to less than 1% of ΔE (MP2). Less symmetrical polyligated complexes (D. R. Garmer, unpublished computations) did not provide significant enough increases to justify their tentative modeling in our procedure. This will not prejudice their importance in the case of open-shell divalent cations, which will be investigated in a future work.

M^{2+} -water

In all cation-water complexes, the dication is located along the external bisector of water in the molecular plane. The component analysis of Table I points out that the origin of binding energy differences depends on which dication is being considered. The difference in binding energy for Zn^{2+} versus Mg^{2+} or Cd^{2+} versus Ca^{2+} is mainly due to effects in the E_{ct} term favoring binding of the soft group IIB cations. The sum of E_{c} and E_{e} components making up E_1 tends to cancel out for cations of similar size. However, in comparing binding within a group we observe that the E_1 and E_{pol} terms are most important in favoring the smaller cation. These results generally also hold for the other ligands although the numerical values for energy differences can vary greatly.

Table I also indicates that these absolute energies and selectivity trends are predicted accurately by the SMM computations. We have also plotted

TABLE Ia.

Mg²⁺-Ligand Complexes: Comparison of SCF / RVS and SMM Binding Energies in Their Optimized Configurations (Energies in kcal / mole, Distances in Ångstroms).

	Neutral Ligands			
	H ₂ O ^a	H ₂ NCHO	Imidazole ^a	CH ₃ SH
<i>R</i>	1.9	1.80	2.0	2.4
<i>θ</i>		165°		
<i>φ</i>				105°
ΔE (SCF)	-79.4	-128.0	-128.6	-86.8
E_c	-66.1	-100.2	-101.1	-45.9
E_e	22.7	35.9	41.0	24.3
E_1	-43.4	-64.3	-60.1	-21.6
E_{pol}	-33.3	-59.7	-65.0	-59.8
E_{ct}	-2.8	-4.0	-3.5	-5.4
E_2	-36.1	-63.7	-68.5	-65.2
ΔE (SMM)	-79.5	-128.6	-127.2	-81.2
E_{MTP}	-63.5	-92.0	-85.6	-45.7
E_{rep}	20.5	24.8	24.8	21.7
E_1	-43.0	-67.2	-60.8	-24.0
E_{pol}	-33.5	-58.1	-61.7	-54.7
E_{ct}	-3.0	-3.3	-4.7	-2.5
E_2	-36.5	-61.4	-66.4	-57.2
	Anionic Ligands			
	HCOO ^{-b}	OH ^{-c}	CH ₃ O ⁻	CH ₃ S ⁻
<i>R</i>	1.94	1.70	1.70	2.1
<i>θ</i>		180°	180°	105°
ΔE (SCF)	-368.1	-393.5	-374.6	-345.6
E_c	-370.8	-405.0	-369.2	-336.0
E_e	86.6	73.5	67.8	80.2
E_1	-284.2	-331.5	-301.4	-255.8
E_{pol}	-72.1	-50.4	-64.4	-75.2
E_{ct}	-8.0	-11.5	-8.8	-14.8
E_2	-80.1	-61.9	-73.2	-90.0
ΔE (SMM)	-361.0	-387.3	-377.7	-340.2
E_{MTP}	-359.4	-381.8	-369.6	-331.3
E_{rep}	77.7	51.7	58.9	82.8
E_1	-281.7	-330.2	-310.7	-248.5
E_{pol}	-71.3	-50.6	-59.7	-82.3
E_{ct}	-8.0	-6.5	-7.2	-9.4
E_2	-79.3	-57.1	-66.9	-91.7

^a External bisector of O (water) or N (Imidazole).

^b The cation bridges the two anionic oxygens in the formate plane.

^c The optimized SMM θ angle is 135° ($\Delta E_{SMM} = -401.7$ kcal / mol; $\Delta E_{SCF} = -392.3$ kcal / mol).

TABLE Ib.

Ca²⁺-Ligand Complexes: Comparison of SCF / RVS and SMM Binding Energies in Their Optimized Configurations (Energies in kcal / mole, Distance in Ångstroms).

	Neutral Ligands			
	H ₂ O ^a	H ₂ NCHO	Imidazole ^a	CH ₃ SH
<i>R</i>	2.3	2.10	2.3	2.8
<i>θ</i>		165°		
<i>φ</i>				120°
ΔE (SCF)	-52.4	-90.7	-85.6	-50.2
E_c	-49.2	-82.1	-77.8	-33.8
E_e	19.0	35.4	38.3	21.1
E_1	-30.2	-46.7	-39.5	-12.7
E_{pol}	-18.1	-36.2	-38.3	-32.1
E_{ct}	-4.1	-7.8	-7.8	-5.4
E_2	-22.2	-44.0	-46.1	-37.5
ΔE (SMM)	-52.7	-91.7	-87.8	-50.8
E_{MTP}	-45.1	-72.9	-66.5	-27.7
E_{rep}	14.9	23.2	26.2	15.3
E_1	-30.2	-49.7	-40.3	-12.4
E_{pol}	-18.5	-35.1	-39.8	-34.2
E_{ct}	-4.0	-7.0	-7.6	-4.2
E_2	-22.5	-42.1	-47.4	-38.4
	Anionic Ligands			
	HCOO ^{-b}	OH ^{-c}	CH ₃ O ⁻	CH ₃ S ⁻
<i>R</i>	2.20	1.90	1.90	2.5
<i>θ</i>		180°	180°	120°
ΔE (SCF)	-309.7	-333.2	-314.8	-277.0
E_c	-321.8	-368.0	-336.9	-289.9
E_e	71.2	93.5	86.7	74.4
E_1	-250.6	-274.6	-250.2	-215.5
E_{pol}	-40.6	-32.2	-42.0	-42.4
E_{ct}	-15.0	-26.4	-22.6	-19.1
E_2	-55.6	-58.6	-64.6	-61.5
ΔE (SMM)	-301.3	-325.0	-308.4	-285.5
E_{MTP}	-314.0	-346.5	-332.9	-271.2
E_{rep}	76.3	80.7	93.5	61.5
E_1	-237.6	-265.9	-239.4	-209.7
E_{pol}	-41.9	-33.9	-40.5	-53.0
E_{ct}	-21.8	-25.2	-28.5	-22.8
E_2	-63.7	-59.1	-69.0	-75.8

^a External bisector of O (water) or N (Imidazole).

^b The cation bridges the two anionic oxygens in the formate plane. Optimized ΔE_{SMM} at 2.3 Å, amounting to -308.9 kcal / mol, corresponding $\Delta E_{SCF} = -307.7$ kcal / mol.

^c The optimized SMM θ angle is 135° ($\Delta E_{SMM} = -329.8$ kcal / mol; $\Delta E_{SCF} = -329.3$ kcal / mol).

TABLE 1c.
 Cd^{2+} -Ligand Complexes: Comparison of the SCF / RVS and SMM Binding Energies in Their Optimized Configurations (Energies in kcal / mole, Distances in Ångstroms).

	Neutral ligands			
	H_2O^a	H_2NCHO	Imidazole ^a	CH_3SH
<i>R</i>	2.2	2.0	2.1	2.5
θ		150°		
ϕ				105°
ΔE (SCF)	-63.8	-103.0	-114.7	-85.6
E_c	-58.5	-90.1	-95.4	-47.0
E_e	27.5	42.1	53.6	35.9
E_1	-31.0	-48.0	-41.8	-11.7
E_{pol}	-23.9	-41.9	-50.4	-43.7
E_{ct}	-8.9	-13.1	-22.5	-30.8
E_2	-32.8	-55.0	-72.9	-74.5
ΔE (SMM)	-61.5	-100.0	-118.2	-89.9
E_{MTP}	-48.9	-81.7	-78.4	-41.0
E_{rep}	18.7	36.0	36.6	27.4
E_1	-30.2	-45.8	-41.8	-13.6
E_{pol}	-22.5	-42.1	-50.7	-46.0
E_{ct}	-9.0	-13.0	-22.8	-30.3
E_2	-31.5	-55.1	-73.5	-76.3

	Anionic ligands			
	HCOO^-^b	OH^-^c	CH_3O^-^d	CH_3S^-
<i>R</i>	2.20	2.0	1.90	2.5
θ		120°	135°	105°
ΔE (SCF)	-335.6	-363.2	-335.2	-344.2
E_c	-327.5	-377.3	-366.7	-325.4
E_e	65.8	84.1	114.4	98.9
E_1	-261.7	-293.2	-252.3	-226.5
E_{pol}	-47.9	-30.3	-44.0	-50.2
E_{ct}	-26.1	-39.7	-38.9	-67.4
E_2	-74.0	-70.0	-82.9	-117.6
ΔE (SMM)	-332.6	-358.5	-326.3	-367.9
E_{MTP}	-309.4	-347.0	-337.8	-303.6
E_{rep}	54.7	55.4	85.7	76.5
E_1	-254.7	-291.5	-252.1	-227.1
E_{pol}	-46.6	-34.2	-40.0	-66.0
E_{ct}	-31.3	-32.7	-37.7	-74.9
E_2	-77.9	-66.9	-77.7	-140.9

^a External bisector of O (water) or N (Imidazole).

^b The cation bridges the two anionic oxygens in the formate plane. Optimized ΔE_{SMM} at 2.3 Å, amounting to -308.9 kcal / mol, corresponding $\Delta E_{\text{SCF}} = -307.7$ kcal / mol.

^c The optimized SMM θ angle is 135° ($\Delta E_{\text{SMM}} = -360.0$ kcal / mol; $\Delta E_{\text{SCF}} = -361.3$ kcal / mol).

^d The optimized SMM θ angle is 180° ($\Delta E_{\text{SMM}} = -331.0$ kcal / mol; $\Delta E_{\text{SCF}} = -332.1$ kcal / mol).

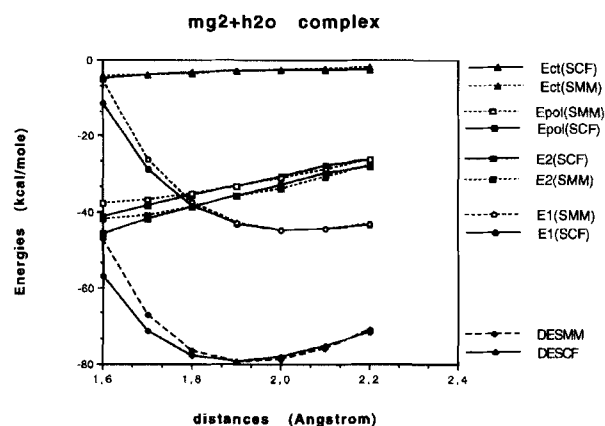


FIGURE 1a. $\text{M}^{2+}-(\text{H}_2\text{O})$. Evolutions of the SCF and SMM binding energies in the Mg^{2+} (a), Ca^{2+} (b*), and Cd^{2+} (c*) complexes, as a function of the O— M^{2+} distance. (Figures 1b* and 1c* are in Supplementary Material.)

the *ab initio* and SMM components for a range of coordination distances in Figures 1a, b*, and c* (asterisk indicates Supplementary Material). These show good agreement until a significant climb is made up due to the repulsive inner wall of the potential energy surface.

M^{2+} -formamide

Formamide binds dications more strongly than water due to an increase in the magnitude of each attractive energy component. However, this ligand has cation selectivity factors reasonably close to those of water. The soft cations bind further away from the carbonyl axis and closer to an idealized lone pair position. This mode of binding appears to generally favor E_{ct} over E_1 , which partly provides the variation between IIA and IIB results. However, the total energy function as a function of the $\theta = \text{C}-\text{O}-\text{M}^{2+}$ angle (see Chart I below) is reasonably flat as shown in Figure 2a and b* for Mg^{2+} and Cd^{2+} , respectively. Figure 2 also illustrates that the SMM function can perform very well even for geometry modes having smooth potential energies. The SMM procedure reproduces the significant increases in electrostatics and polarization responses compared with water.

M^{2+} -imidazole

In their complexes with imidazole, the dications always lie along the nitrogen lone pair position, and there is a significant energetic cost for variations away from it which precludes these from

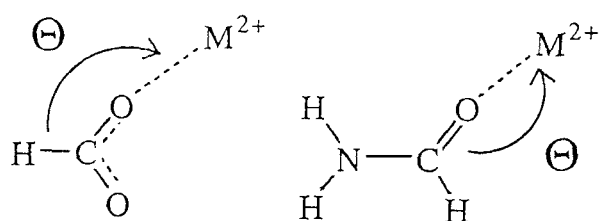


CHART I.

occurring in biomolecules (see, e.g., Ref. 2). The binding affinities of imidazole for IIA cations are similar to formamide except for some increase in the magnitude of E_2 , compensated by a decrease in E_1 , whether these terms are computed *ab initio* or by the SMM procedure. The increased role of E_{ct} in E_2 is more significant for IIB cations and thus leads to a preference for binding soft cations from either type of calculation. This preference is borne out by observed trends in proteins where coordination spheres with imidazole ligands invariably bind softer cations.

M^{2+} -methanethiol

Methanethiol is a ligand functional group encountered in protonated cysteine or methionine side-chains. Optimization at the Hartree-Fock level predicts that all cations lie along a sulfur lone pair. As conforms to our previous results on Zn^{2+} -methanethiol,² such a preference is reproduced by the SMM computations. The binding energies exceed those for water primarily because of an increased magnitude for E_2 components. Such an

increase is particularly accented in the case of the IIB cation Cd^{2+} , comparable to the one previously put forth in the case of Zn^{2+} .^{2,5,8} Whereas the magnitude of E_2 is underestimated by the SMM computations in the case of the Mg^{2+} complex, it is reproduced to better than 3% by this procedure for the other dications.

M^{2+} -formate

In their optimized binding configurations, the divalent cations bridge both anionic oxygens in the formate plane [see, e.g., Refs. 2, 5, 7(a), 8, and references therein]. In their polyligated complexes which involve aspartate or glutamate protein side chains, the dications are generally bound in a monodentate fashion to one anionic oxygen, with $\theta = C-O-M^{2+}$ angles, amounting to approximately 120° . As a complement to Table I, we have indicated, in Tables II a, b, and c*, the compared SCF/SMM binding energies of Mg^{2+} , Ca^{2+} , and Cd^{2+} for monodentate binding, upon performing stepwise 30° variations of the $\theta = C-O-M^{2+}$ angle. In the starting position ($\theta = 120^\circ$), $O-M^{2+}$ is *cis* to the $C-H$ bond (see chart II). For this representative θ value, energy-optimization by the SCF method yielded $O-M^{2+}$ distances 0.15–0.20 Å shorter than in the corresponding bridging positions, and this was also obtained by the SMM

TABLE IIa.
 Mg^{2+} -Formate: Comparison of SCF / RVS
and SMM Binding Energies As a Function of
 $\theta = C-O-Mg^{2+}$ Angle ($O-Mg^{2+}$ Distance Is
Set at 1.79 Å; $\theta = 120^\circ$, Corresponds to the
 $O-Mg^{2+}$ Bond *cis* to $H-C$ One).^a

	$\theta = 120^\circ$	$\theta = 150^\circ$	$\theta = 180^\circ$	$\theta = 210^\circ$	$\theta = 240^\circ$
ΔE (SCF)	-311.8	-317.8	-321.6	-326.7	-337.1
E_c	-309.9	-303.0	-299.6	-309.9	-330.9
E_θ	62.1	50.5	44.7	48.2	57.5
E_1	-247.8	-252.5	-254.9	-261.7	-273.4
E_{pol}	-56.8	-59.3	-60.3	-58.8	-57.2
E_{ct}	-7.2	-6.0	-6.4	-6.2	-6.5
E_2	-64.0	-65.3	-66.8	-65.0	-63.7
ΔE (SMM)	-321.8	-325.2	-326.6	-333.2	-347.3
E_{MTP}	-303.3	-294.9	-290.6	-302.1	-323.9
E_{rep}	37.6	29.2	25.4	29.2	37.3
E_1	-265.7	-265.7	-265.2	-272.9	-286.6
E_{pol}	-50.2	-54.0	-56.2	-54.8	-54.5
E_{ct}	-5.9	-5.5	-5.2	-5.6	-6.3
E_2	-56.1	-59.5	-61.4	-60.4	-60.8

^a Energies in kcal / mole, angles in degrees.

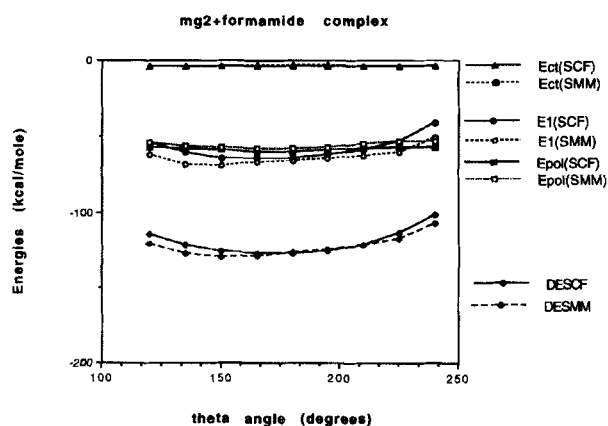


FIGURE 2. M^{2+} -formamide. Evolutions of the SCF and SMM binding energies in the Mg^{2+} (a) and Cd^{2+} (b*) complexes, as a function of the $\theta = C-O-M^{2+}$ angle. (Figure 2b* is in Supplementary Material.)

TABLE IIb.

Ca^{2+} —Formate: Comparison of SCF / RVS and SMM Binding Energies As a Function of $\theta = \text{C—O—Ca}^{2+}$ Angle (O— Ca^{2+} Distance Is Set at 2.06 Å; $\theta = 120^\circ$ Corresponds to the O— Ca^{2+} Bond *cis* to H—C one).^a

	$\theta = 120^\circ$	$\theta = 150^\circ$	$\theta = 180^\circ$	$\theta = 210^\circ$	$\theta = 240^\circ$
ΔE (SCF)	-257.1	-264.6	-269.6	-273.9	-283.4
E_c	-277.9	-272.5	-270.6	-280.0	-300.2
E_e	72.3	59.5	53.0	56.9	67.3
E_1	-205.6	-213.0	-217.6	-223.1	-232.9
E_{pol}	-36.0	-37.4	-38.4	-36.9	-35.9
E_{ct}	-15.5	-14.2	-13.6	-13.9	-14.6
E_2	-51.5	-51.6	-52.0	-50.8	-50.5
ΔE (SMM)	-267.7	-275.3	-278.9	-284.4	-294.3
E_{MTP}	-262.3	-258.3	-257.0	-266.5	-285.5
E_{rep}	44.3	34.2	29.9	34.2	44.4
E_1	-218.0	-224.1	-227.1	-232.4	-241.0
E_{pol}	-32.4	-34.7	-36.3	-35.6	-35.4
E_{ct}	-17.4	-16.4	-15.5	-16.4	-17.9
E_2	-49.8	-51.1	-51.8	-52.0	-53.3

^a Energies in kcal / mole, angles in degrees.

computations. These optimized distances were then held upon incrementing θ . The SMM computations overestimate the binding strength for Mg^{2+} and Ca^{2+} (still, however, by $< 5\%$), but this is consistent for the different geometries. The reproduction of nonmonotonic behavior in all of the energy terms in every important in obtaining this agreement. A more detailed scrutiny of the comparative SCF/SMM energy components as a function of the θ angle was given in Ref. 2 in the case of the Zn^{2+} —formate complex.

The size selectivity effects for cation binding are naturally dominated by the electrostatic term in E_1 . Selectivity between IIA and IIB cations is mostly determined by the E_{ct} term favoring the IIB cations. The SMM calculations reproduce these qualitative trends and the effects of the less dominant terms. The selectivity factors are very consistent for different coordination geometries in either type of calculation. All selectivities are also larger in magnitude than the analogous factors for the neutral oxygen-donor ligands.

M^{2+} —hydroxy

In the case of the complexes of hydroxy with the two IIA cations, a very small energetic preference ($< 2\%$) is found in the SCF computations favoring the colinear arrangement ($\theta = \text{H—O—}$

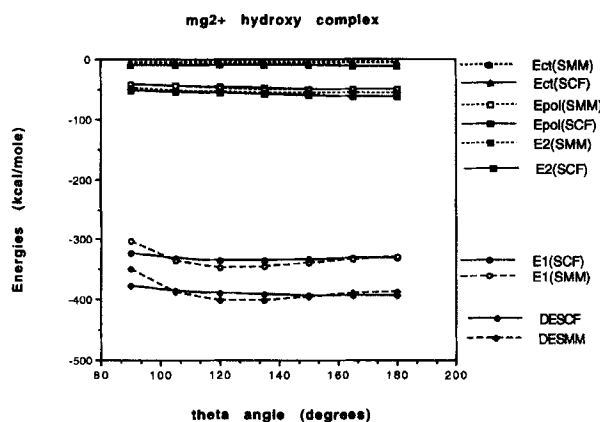


FIGURE 3. Mg^{2+} —hydroxy. Evolutions of the SCF and SMM binding energies as a function of the $\theta = \text{H—O—Mg}^{2+}$ angle.

$\text{M}^{2+} = 180^\circ$). On the other hand, the SMM computations indicate for these two cations a preference in favor of $\theta = 135^\circ$. As shown on Figure 3 for the typical Mg^{2+} — $\text{OH}(-)$ complex, the overall behaviors of ΔE (SCF) and ΔE (SMM) and their individual components, nevertheless, remain extremely flat in the energetically relevant zone ($< 105^\circ < \theta < 180^\circ$). The deviation of ΔE (SMM) with respect to ΔE (SCF) can be traced back to the E_1 component (see Fig. 3). The SMM computations provide a more accurate angular agreement for Cd^{2+} , where both procedures predict that $\theta = 120^\circ$ – 135° . The representation of small energetic trends is probably most difficult for this particular ligand because the contacts with cations are extremely short and strong. With complete coordination shells the coordination is forced to longer distances which could ameliorate the problem to some extent.

Selectivity for cations from this ligand is qualitatively similar to that of bidentate formate although with significant quantitative variations. There is a similar selectivity for smaller cations and for group IIB. These selectivity factors are also more important than for a water ligand so that deprotonation of water coordinated to a IIB cation is easier than for a IIA cation of similar size.

M^{2+} —methoxy

The geometric trends for methoxy at the Hartree-Fock level are similar to the hydroxy anion, although the equilibrium θ is slightly larger for the IIB cations. However, the SMM model now reproduces the correct angular geometry also for the IIA cations with a colinear M^{2+} — O—C bond.

The individual components, *ab initio* or SMM, are changed so that the magnitude of electrostatic interaction is reduced and polarization is increased due to the presence of the methyl group. This does not produce a very significant modulation of any selectivity properties compared with the hydroxy anion.

M^{2+} —methanethiolate

Methanethiolate is encountered as the side chain of deprotonated cysteine residues, and also within the mercaptan class of metalloenzyme inhibitors.¹⁷ It is the most strongly selective for IIB cations and has considerable bond strength as well. The selectivity effect is mainly due to the relatively large E_{ct} component with IIB cations. E_{pol} is also very large but not very selective between IIA and IIB cations of similar size. The large magnitude of these relaxation terms is due to the loose attachment and high polarizability of the diffuse sulfur lone pairs. The optimal binding modes have a sharp M^{2+} —S—C angle of 105–120°. There is an energy cost for variations from the equilibrium as shown in Figure 4a* and b for the Mg^{2+} and Cd^{2+} complexes. This binding mode is therefore found in all known crystal structures having this functional group ligand.

The comparisons of the SCF and SMM results in Table I and in the figures show that the SMM procedure is able to reproduce these trends. Concerning the Cd^{2+} cation, however, a total deviation in energetics of approximately 7% of the total binding energy can be observed, whereas the corresponding Zn^{2+} complex, which was investigated earlier,² had lent itself to a much more accurate agreement. This is due to an addition of smaller errors in components. This is the least satisfactory comparison result in total energies obtained with the current ligand set.

Preliminary calculations on complete coordination spheres formed from methanethiolate and imidazole ligands suggest that the selectivity for Zn^{2+} over Mg^{2+} is on the order of 40 kcal/mol greater than for a hydrate model such as M^{2+} (H_2O)₆ discussed below. Therefore, it is not surprising that binding of hard cations to these sites in proteins such as zinc fingers has not been observed experimentally. The IIA coordination distances are also relatively long compared with IIB cations. In contrast, the hydrates and other hard ligand species give almost equal coordination distances for Mg^{2+} and Zn^{2+} . Studies of several complete first-shell models will be reported elsewhere.

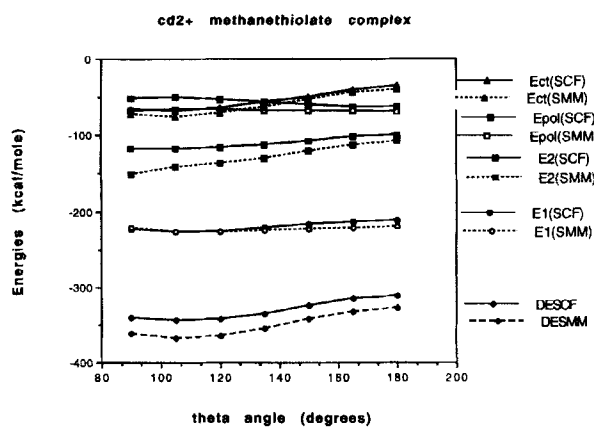


FIGURE 4b. M^{2+} —methanethiolate. Evolutions of the SCF and SMM binding energies in the Mg^{2+} (a*) and Cd^{2+} (b) complexes as a function of the $\theta = C-S-M^{2+}$ angle. (Figure 4a* is in Supplementary Material.)

Inclusion of an Explicit Dispersion-Energy Term

As mentioned in the Introduction, an explicit E_{disp} term was only incorporated, in the SMM computations, for Zn^{2+} and Cd^{2+} , since the MP2 correlation energy was computed to be very small in the case of Mg^{2+} and Ca^{2+} .⁵ A comparison between E_{disp} (SMM) and E_{corr} (*ab initio* SCF/MP2, Ref. 5) is given in Table III. For Zn^{2+} , E_{disp} (SMM) can satisfactorily reproduce E_{corr} , except in the case of formamide and methoxy. For Cd^{2+} , in addition to its formamide complex, all anionic complexes give rise to strongly exaggerated values of E_{disp} , particularly in the case of hydroxy and methoxy. These misfits may translate the onset of more complex phenomena in the MP2 procedure that could be possibly accounted for by the formulation of E_{disp} (SMM). Also, an expansion of the Moller-Plesset procedure beyond the MP2 level may be warranted in some cases to further assess this point. Note that the equilibrium distances at which these comparisons were carried out are generally short. It is expected that since, in polyligated complexes, the cation–ligand distances will increase due to the interligand repulsions, the numerical misfits should be reduced faster (as $1/R^* \cdot 6$) than the accumulation of errors caused by the larger number of ligands.

E_{disp} reproduces the trends of E_{corr} (MP2) by increasing upon passing from O- to N- to S-con-

TABLE III.
 Zn^{2+} and Cd^{2+} Ligand Complexes. Comparison Between Values of E_{disp} (SMM) and of Large-Basis-Set *Ab Initio* Correlation Energy MP2 of Ref. 5.^a

	H_2O	CH_3OH	H_2NCHO	Imidazole	CH_3SH
Neutral complexes					
Zn^{2+}					
E_{disp} (SMM)	-7.2	-8.1	-9.9	-13.4	-14.2
E_{corr} (MP2)	-6.9	-9.2	-6.0	-15.4	-17.7
R	1.90	1.88	1.80	1.89	2.31
Cd^{2+}					
E_{disp} (SMM)	-6.4	-7.9	-9.9	-13.7	-19.3
E_{corr} (MP2)	-6.4	-8.9	-5.7	-16.0	-17.7
R	2.15	2.13	2.05	2.11	2.53
	HCOO^-	CH_3O^-	OH^-	CH_3S^-	
Anionic complexes					
Zn^{2+}					
E_{disp} (SMM)	-15.1	-14.4	-18.1	-29.3	
E_{corr} (MP2)	-18.4	-21.6	-19.0	-28.7	
R	1.98	1.75	1.75	2.18	
Cd^{2+}					
E_{disp} (SMM)	-15.1	-12.9	-12.0	-24.9	
E_{corr} (MP2)	-19.7	-24.0	-21.4	-31.2	
R	2.19	1.97	1.97	2.39	

^a Energies in kcal/mol.

taining ligands. Thus, conforming to our previous conclusions,⁵ the dispersion/correlation term, together with the charge-transfer term, are the two contributors to the increase in relative affinities of Zn^{2+} and Cd^{2+} for "soft" ligands, and concomitantly, of the enhanced discrimination, by such ligands, in favor of IIB cations over the IIA cations Mg^{2+} , and Ca^{2+} . We will elaborate on these points further in the next section.

Binding Energies in a Representative Polyligated Complex: $\text{M}^{2+}(\text{H}_2\text{O})_6$

To evaluate how well the SMM procedure can account for the strong nonadditivity effects prevailing in the polyligated complexes of divalent cations (see Refs. 18–20, and references therein), and in line with our previous investigations,^{2,5,8} we have considered representative hexahydrates of Mg^{2+} , Ca^{2+} , Zn^{2+} , and Cd^{2+} . Each cation is surrounded by a first shell of six water molecules, disposed in a regular octahedron. The water planes are rotated to minimize their mutual repulsions through their hydrogen atoms, and the energies

are optimized as a function of the M^{2+} —water distances. The results are reported in Table IV, and the values of ΔE (SMM), including E_{disp} , are compared to those of the corresponding ΔE (SCF/MP2) values published in Garmer and Gresh.⁵ A close numerical agreement (< 3%) can be seen. The SMM procedure is also able to account for the modest increases of M^{2+} —O distances, which occur upon addition of five water molecules. Note the restricted increase of E_{pol} (SMM) and E_{ct} (SMM). Thus, as pointed out earlier,^{2,8} these two components increase by only factors of approx. 2.6 and 2, respectively, with respect to the monoligated case at the same M^{2+} —O distance, even though the number of ligands increases by six. This reflects the corresponding behaviors of the SCF components.

Ion Selectivity Trends as Function of Binding Energy Components

Given a pair of two divalent cations, we have, in our previous investigation,⁵ monitored the evo-

TABLE IV.

Hexahydrates of Mg^{2+} , Ca^{2+} , Zn^{2+} , and Cd^{2+} (Energies in Kcal/mol, Distances in Ångstroms).

	$\text{Mg}^{2+}(\text{H}_2\text{O})_6$	$\text{Ca}^{2+}(\text{H}_2\text{O})_6$	$\text{Zn}^{2+}(\text{H}_2\text{O})_6$		$\text{Cd}^{2+}(\text{H}_2\text{O})_6$
$d\text{M}^{2+}\cdots\text{O}$	2.10	2.44	2.10	2.15	2.36
ΔE	-318.5	-234.1	-350.1	-347.2	-280.0
E_1	-229.3	-170.5	-219.7	-222.5	-175.8
E_{pol}	-76.0	-50.4	-82.8	-81.7	-58.9
E_{ct}	-4.2	-9.2	-13.7	-13.2	-15.3
E_2	-80.2	-59.6	-96.5	-94.9	-74.2
E_{disp}	-8.9	-4.0	-33.8	-29.8	-30.0
ΔE (MP2) ^a	-325.0	-244.7	-346.6		-290.7

^a *Ab initio* MP2 computations of Ref. 5.

lution of their differential binding energetics as a function of the softness/hardness of the bound ligand. The purpose of this section is to assess the extent to which the SMM procedure is able to reproduce the trends of this SCF/MP2 analysis. For that purpose, we will consider the same three pairs as in Ref. 5, namely: (a) Zn^{2+} vs. Mg^{2+} , as representative of two cations of comparable ionic size but belonging to two distinct groups, IIA and IIB; (b) Mg^{2+} vs. Ca^{2+} ; and (c) Zn^{2+} vs. Cd^{2+} , as representative of two cations of different ionic sizes within groups IIA and IIB respectively. As in Ref. 5, the ligands are ranked along the scale of their increasing "softness," namely: water < methanol < formamide < methylamine < imidazole < formate < hydroxy < methoxy < methanethiol < methanethiolate. The results are reported in Figure 5a, b, and c*, in which, similar to Ref. 3, we have plotted on the ordinates the differences, $\delta[\Delta E (\text{SMM})]$, of equilibrium binding energies between the considered pair of cations as well as the differences, δ , between relevant energy components.

Zn^{2+} VS. Mg^{2+}

The evolution of $\delta[\Delta E (\text{SMM})]$ along the scale of ligands considered (Fig. 5a) presents the same shape as that of the corresponding curve of $\delta[\Delta E (\text{SCF/MP2})]$ published in Ref. 5. The only difference resides in a local maximum occurring with methoxy, whereas $\delta[\Delta E (\text{SCF/MP2})]$ plateaus for this anion. Note the presence of a small indentation occurring for formate, similar to the one found in the SCF/MP2 analysis, and the closely similar values of $\delta[\Delta E (\text{SMM})]$ for methanethiol and hydroxy, as was the case of $\delta[\Delta E (\text{SCF/MP2})]$. With the exception of the hydroxy case, $\delta(E_1)$ presents a

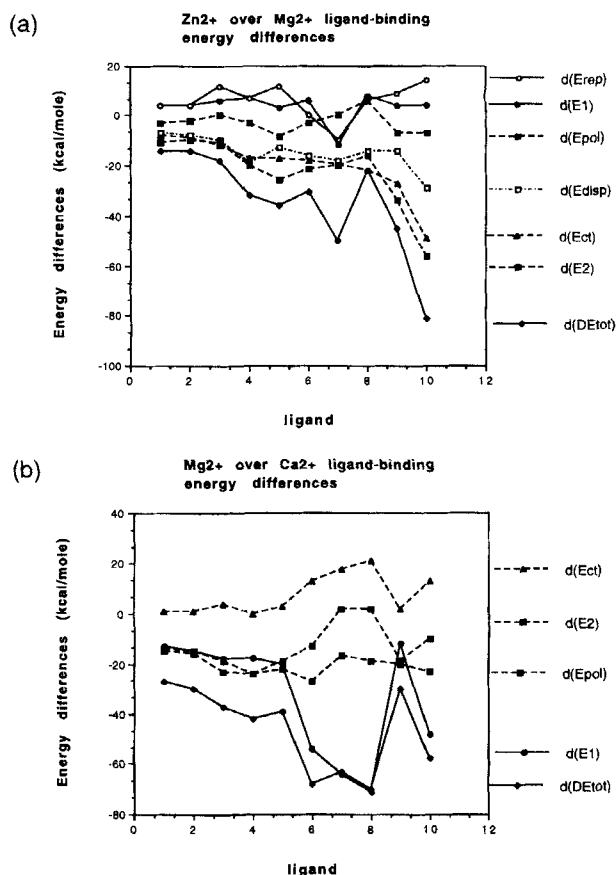


FIGURE 5. 1 = H_2O ; 2 = CH_3OH ; 3 = formamide; 4 = CH_3NH_2 ; 5 = imidazole; 6 = formate; 7 = OH^- ; 8 = CH_3O^- ; 9 = CH_3SH ; 10 = CH_3S^- —for the following: (a) Selectivity from the SMM binding energies and components for Zn^{2+} over Mg^{2+} . (b) Selectivity from the SMM binding energies and components for Mg^{2+} over Ca^{2+} . (c*) Selectivity from the SMM binding energies and components for Zn^{2+} over Cd^{2+} (Figure 5c* is available as Supplementary Material).

flat behavior for the whole range of ligands irrespective of their hardness/softness character and ionization state. The shapes of $\delta(E_{\text{rep}})$ and $\delta(E_{\text{pol}})$, although more accented, offer no correlation with that of $\delta[\Delta E (\text{SMM})]$. The latter is essentially dictated by that of the two second-order components, $\delta(E_{\text{ct}})$ and $\delta(E_{\text{disp}})$. Consistent with the SCF/MP2 analysis, the numerical weight of $\delta(E_{\text{ct}})$ is slightly greater than that of $\delta(E_{\text{disp}})$, and becomes more pronounced with methanethiol and methanethiolate.

Mg^{2+} VS. Ca^{2+}

The evolution of $\delta[\Delta E (\text{SMM})]$ along the scale of ligands considered (Fig. 5b) offers a striking contrast to that of the Zn^{2+} vs. Mg^{2+} pair. It closely reproduces that of $\delta[\Delta E (\text{SCF/MP2})]$ with the exception that $\delta[\Delta E (\text{SMM})]$ is the greatest with the three anionic O-containing ligands instead of methanethiolate. Its shape is now dictated by that of the first-order term $\delta(E_1)$, and is a reflection of "size selectivity." It is very instructive to observe that, whereas $\delta(E_{\text{pol}})$ exhibits a flat behavior, the shape of $\delta(E_{\text{ct}})$ is nearly exactly opposite to that of $\delta(E_1)$, again similar to the behavior of $\delta[E_{\text{ct}} (\text{SCF})]$.

Zn^{2+} VS. Cd^{2+}

The evolution of $\delta[\Delta E (\text{SMM})]$ (Fig. 5c*) exhibits a very similar shape to that of the Mg^{2+} vs. Ca^{2+} pair, and also to that of the corresponding $\delta[\Delta E (\text{SCF/MP2})]$ curve.⁵ Among anionic ligands, $\delta[\Delta E (\text{SMM})]$ is larger with the three O-containing ligands than with methanethiolate, consistent with the SCF/MP2 results. The shape of $\delta[\Delta E (\text{SMM})]$ is dictated by that of $\delta(E_1)$, exemplifying again the size selectivity discrimination, whereas again the shape of $\delta(E_{\text{ct}})$ is opposite to that of $\delta[\Delta E (\text{SMM})]$.

Conclusions

The SMM procedure has recently been refined to treat peptide and peptide-like molecules, as well as their interactions with Zn^{2+} .² The present investigation extends the realm of application of this procedure to the divalent cations Mg^{2+} , Ca^{2+} , and Cd^{2+} . We performed a survey of representative complexes of these cations with neutral and anionic ligands encountered in biological complexes. This was done by monitoring the evolu-

tions of the separate SMM energy components E_1 , E_{pol} , and E_{ct} , as a function of radial and angular variations. These energy terms were shown to closely match their *ab initio* SCF counterparts obtained at the outcome of an energy decomposition with the restricted variational space analysis,¹ and the overall numerical agreement of $\Delta E (\text{SMM})$ with $\Delta E (\text{SCF})$ was to within $< 3\%$. An explicit dispersion energy term was subsequently incorporated in the case of the two IIB cations, Zn^{2+} and Cd^{2+} , enabling for these two cations the results of the SMM procedure to be compared to *ab initio* computations carried out at the MP2 level.⁵ As models for their polyligated complexes with neutral ligands, hexahydrates of the four cations, $\text{M}^{2+}(\text{H}_2\text{O})_6$, were then investigated, with each cation being located in the center of a regular octahedron. The SMM results could, again, reproduce the SCF/MP2 ones to within $< 3\%$. The strong nonadditive character of the two second-order terms, $E_{\text{ct}} (\text{SMM})$ and $E_{\text{pol}} (\text{SMM})$, was put forward, consistent with our previous analysis of Zn^{2+} -polyligated complexes.^{5,8} Finally, using the SMM procedure, we undertook a survey of ion-selectivity trends as a function of the energy components. The evolution of the Zn^{2+} vs. Mg^{2+} differences as a function of ligand "softness" was ascribed to the two second-order terms, E_{ct} and E_{disp} . A more important role of the latter is anticipated in polyligated complexes, in view of the strong nonadditive character of E_{ct} . On the other hand, the evolutions of both Mg^{2+} vs. Ca^{2+} , and Zn^{2+} vs. Cd^{2+} differences were due to the first-order term, E_1 , with a contravariant evolution of the charge-transfer term. For these three ion couples, the SMM analyses reflected closely the SCF/MP2 ones which were published earlier.⁵

The encouraging results obtained with the SMM procedure, bearing on the four closed-shell divalent cations Mg^{2+} , Ca^{2+} , Zn^{2+} , and Cd^{2+} , in addition to those on several recently reported neutral and ionic H-bonded complexes,¹⁵ stimulate the prospect of large-scale applications to biologically and pharmacologically relevant problems. Comparisons between the SMM and the RVS/MP2 procedures which involved tetra- and hexaligated complexes of Mg^{2+} and Zn^{2+} with two anionic ligands (Garmer and Gresh, manuscript in preparation) were also highly encouraging. Applications are under way which bear on inhibitor-metalloenzyme- Zn^{2+} complexes within the binding cleft of native and mutated metalloproteases (Ref. 17 and references therein), as well as the complexes of Zn^{2+} within its binding loop in Zn

finger proteins.²¹ In light of the present SMM vs. SCF comparisons, related applications could be readily envisaged with the Mg^{2+} and Ca^{2+} cations as well. The Langlet-Claverie reaction field procedure²² is also available to account for solvation/desolvation effects in computations of detailed energy balances.²³ Consistent with the SMM procedure, it computes both electrostatic and polarization contributions to solvation by means of the distributed *ab initio* SCF multipoles. It is presently operational on our computer code, which has been submitted to QCPE for release.

Supplementary Material

Figures 1b*, 1c*, 2b*, 4a*, and 5c*, and Table IIc* marked with an asterisk in the text are available from the authors upon request, or via the Internet in Supplementary Material (see footnote * on page 1481).

Acknowledgments

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Appendix

VALUES OF PARAMETERS USED IN CALIBRATION OF Mg^{2+} , Ca^{2+} , AND Cd^{2+}

Parameters Used in Expression of E_{rep}

	W	K (M—H)	K (M—C)	K (M—N)	K (M—O)	K (M—S)	m_{PM}
Mg^{2+}	1.265	11.7	11.6	12.9	14.0	11.0	1.0 ^a 1.87 ^b
Ca^{2+}	1.475	25.8	25.8	28.5	31.4	19.3	1.0 ^a 1.87 ^b
Cd^{2+}	1.455	22.9	22.9	25.4	27.5	11.6	1.0 ^a 1.87 ^b

(a) oxygen or nitrogen ligand.

(b) sulfur ligand.

Parameters Used in Expression of E_{ct}

	U_{M}	S_{M}	D_{M}	t_{AsM}	t_{ApM}	m_{AM}
Mg^{2+}	2.0	0.95	2.50	0.59 ^a 0.53 ^b 0.53 ^c	0.59 ^a 0.53 ^b 0.53 ^c	0.37 ^a 0.29 ^b 0.50 ^c
Ca^{2+}	1.7	2.00	4.50	0.59 ^a 0.54 ^b 0.50 ^c	0.59 ^a 0.54 ^b 0.50 ^c	0.37 ^a 0.30 ^b 0.69 ^c
Cd^{2+}	1.9	5.00	2.50	0.39 ^a 0.33 ^b 0.31 ^c	0.57 ^a 0.51 ^b 0.51 ^c	0.57 ^a 0.52 ^b 0.90 ^c

^a A = nitrogen atom.

^b A = oxygen atom.

^c A = sulfur atom.

Parameters Used in Expression of E_{disp}

	$K(\text{M—H})$	$K(\text{M—C})$	$K(\text{M—N})$	$K(\text{M—O})$	$K(\text{M—S})$
Zn^{2+}	2.94	5.85	5.85	3.85	12.00
Cd^{2+}	5.62	11.17	11.17	7.35	22.92

Values of Effective Radii of Heteroatom Centers and on Lone-Pair Extremities used for E_{disp}

	Atom Center	Lone-Pair Extremity
Nitrogen (Imidazole)	1.42	0.30
Oxygen Neutral:		
sp^3	1.28	0.97
sp^2	1.24	0.95
Anionic:		
Carboxylate (e.g., formate)	1.26	0.95
Methoxy sp^3	1.42	0.95
Hydroxylate	1.73	0.95
Sulfur Neutral (Methanethiol)	1.93	1.55
Anionic (Methanethiolate)	2.40	1.30

References

- W. J. Stevens and W. Fink, *Chem. Phys. Lett.*, **139**, 15 (1987).
- N. Gresh, *J. Comput. Chem.*, **16**, 856 (1995).
- H. Sigel, Ed., *Metal Ions in Biological Systems*, (a) vol. 20, (1986), (b) vol. 23 (1989), and (c) vol. 24 (1990).
- R. Parr and R. G. Pearson, *J. Am. Chem. Soc.*, **105**, 7512 (1983).
- D. R. Garmer and N. Gresh, *J. Am. Chem. Soc.*, **116**, 3556 (1994).

6. (a) N. Gresh, P. Claverie, and A. Pullman, *Theor. Chim. Acta*, **66**, 1 (1984); (b) N. Gresh, A. Pullman, and P. Claverie, *Theor. Chim. Acta*, **67**, 11 (1985).
7. (a) N. Gresh, P. Claverie, and A. Pullman, *Int. J. Quantum Chem.*, **29**, 101 (1986); (b) N. Gresh, A. Pullman, and P. Claverie, *Int. J. Quantum Chem.*, **28** 757 (1985).
8. N. Gresh, W. J. Stevens, and M. Krauss, *J. Comput. Chem.*, **16**, 843 (1995).
9. W. J. Stevens, H. Basch, and M. Krauss, *J. Chem. Phys.*, **81**, 6026, (1984).
10. L. J. Bartolotti, L. G. Pedersen, and P. S. Charifson, *J. Comput. Chem.*, **12**, 1125 (1991).
11. F. Vigné-Maeder and P. Claverie, *J. Chem. Phys.*, **88**, 4988 (1988).
12. D. R. Garmer and W. J. Stevens, *J. Phys. Chem.*, **93**, 8263 (1989).
13. S. Creuzet, J. Langlet, and N. Gresh, *J. Chim. Phys.*, **88**, 2399 (1991).
14. O. Hess, M. Caffarel, J. Langlet, C. Huiszoon, and P. Claverie, in *Modelling of Molecular Structures and Properties*, J.-L. Rivail, Ed., **71**, 323 (1990).
15. N. Gresh, M. Leboeuf, and D. R. Salahub, in *Modeling the Hydrogen Bond*, American Chemical Society Symposia, vol. **569**, D. A. Smith, Ed., p. 81, (1994).
16. G. Corongiu and E. Clementi, *J. Chem. Phys.*, **69**, 4885 (1978).
17. B. P. Roques, F. Noble, V. Dauge, M.-C. Fournié-Zaluski, and A. Beaumont, *Pharmacol. Rev.*, **45**, 88 (1993).
18. L. Ortega-Blake, O. Novaro, A. Les, and S. Rybak, *J. Chem. Phys.*, **76** 5405 (1982).
19. L. A. Curtiss, J. W. Halley, and J. Hautman, *Chem. Phys. Lett.*, **133**, 89 (1989).
20. J. Caldwell, I. Dang, and P. A. Kollman, *J. Am. Chem. Soc.*, **112**, 9144 (1990).
21. N. Morellet, H. de Rocquigny, Y. Mély, N. Jullian, H. Déméné, M. Ottmann, D. Gérard, J.-L. Darlix, M.-C. Fournié-Zaluski, and B. P. Roques, *J. Mol. Biol.*, **235**, 287 (1992).
22. J. Langlet, P. Claverie, J. Caillet, and A. Pullman, *J. Phys. Chem.*, **92**, 1617 (1988).
23. J. Langlet, N. Gresh, and C. Giessner-Prettre, *Biopolymers* **36**, 765 (1995).